

**AMENDMENT TO THE SPECIFICATION**

Please replace the paragraph beginning at page 10, line 19 with the following paragraph:

--Figure 14A and Figure 14B (SEQ ID NO:14) show sequences for the  
Pst 1 and Pac 1 sites, as described in Example 1.--

**Formalities**

Claims 1-31 are pending in the instant application. Claims 27-28 were withdrawn from consideration as being drawn to a nonelected invention. Claims 1-26 and 29-31 were examined, and were rejected by the Examiner.

Claims 1, 8, 18, 20-26, and 29-31 have been amended. Claim 11 has been canceled. In light of the amendments to the claims, reconsideration and allowance are respectfully requested.

Support for the amendment to claims 1, 18, 20, 22, 26, 29 and 30 can be found throughout the specification, at, for example, page 8, lines 15-19, page 12, line 20 through page 15 line 6, and at page 18, line 18 through page 19, line 26. Claims 8, 20 and 23-25 were amended merely to correct claim dependencies. As such, no new matter has been added.

The specification was amended at the Brief Description of the Drawings (Figure 14A and B) in order to include a sequence identifier so that the application is in sequence compliance, as noted below. The sequence described in the Figure was included in the originally filed application, and is now properly incorporated into the sequence listing for this application. As such the amendment to the specification does not constitute new matter.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

**Sequence Compliance**

The Examiner has objected to the specification for allegedly failing to comply with the requirements of 37 C.F.R. §1.821 through 1.825. In particular, the Examiner has asserted that the sequence shown in Figure 14 does not have a corresponding sequence in the sequence listing.

Applicants submit that the sequence disclosed in Figure 14 (A-B) is the sequence intended to be set forth in SEQ ID NO:14 of the sequence listing filed previously. However, the last 659 nucleotides were inadvertently omitted from the corresponding sequence (SEQ ID NO:14) in the previously filed sequence listing.

In order to comply with the requirements set forth in 37 C.F.R. §1.821 through 1.825, Applicants submit a substitute sequence listing in paper and computer readable form pursuant to 37 C.F.R. §1.821(c) and (e). Applicants hereby state that the content of the paper and computer readable copies of the sequence listing submitted in this application are the same. Moreover, as the sequence listing merely presents nucleotide and/or amino acid sequences that appeared in the application as originally filed in accordance with 37 C.F.R. §1.821-1.825, no new matter has been introduced into the application.

Accordingly, Applicants respectfully request the entry of the paper and computer readable forms of the substitute sequence listing into the application.

Applicants believe that the instant application is now in compliance with the requirements of 37 C.F.R. §1.821 through 1.825.

#### **Rejections under 35 U.S.C. § 112, first paragraph**

Claims 1-25 and 29-31 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

The claims recite a targeting construct comprising a positive selection marker, two regions of homology to a target sequence and a “regulator” that controls expression of the positive selection marker. The Examiner has asserted that the claims encompass an enormous genus of targeting constructs comprising a “regulator” comprising literally any protein or DNA sequence, or combination thereof, arranged in any fashion on the targeting construct.

Applicants submit that the amendments to the claims made by this amendment overcome the Examiner’s rejection. More particularly, the claims now recite function and properties of the regulator. Applicants have described, and the skilled artisan would envision, many combinations of selectable markers and regulators capable of use in the present invention (see, for example, pages 12-14 of the specification). Such a regulator molecule controls the expression of the selectable marker such that the skilled artisan could create a situation in which he/she could enrich a cell population containing proper incorporation of the targeting vector in accordance with the present invention.

The Examiner has also asserted that the specification does not describe other arrangements of the targeting construct as encompassed by the claims. This aspect of the

rejection has also been overcome by the amendments to the claims. The claims now recite the arrangement of the components of the targeting construct with regard to the location of the two homologous sequences relative to the other components of the targeting construct.

As the rejection under 35 U.S.C. §112, first paragraph, has been overcome by the amendments above, Applicants request withdrawal of the rejection. Applicants submit that the pending claims are patentable and fully comply with the written description requirements set forth in 35 U.S.C. §112, first paragraph.

### **Rejections under 35 U.S.C. § 112, second paragraph**

The Examiner has rejected claims 1-25 and 29-31 under 35, U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

With regard to each of claims 1-25 and 29-31, the Examiner asserts that the metes and bounds of the term “regulator” are unclear, and that this term renders the claims indefinite. Applicants disagree. However, in light of the amendments to the claims, the meaning of the term regulator is clear. The skilled artisan would know to what types of molecules the term regulator refers in the context of a regulator molecule used to control expression of a selectable marker within a targeting vector. Such regulator molecules have been described by Applicants (see, for example, page 8, lines 15-19 and page 13, lines 1-20) as well as in the art. The amendments to the claims overcome this aspect of the rejection in light of the disclosure of the instant application and knowledge of the skilled artisan with regard to the meaning of the term regulator. The amended claim language makes it clear what type of regulator would satisfy the limitation of the claims as amended.

Regarding claim 20, the Examiner has asserted that the phrase “introducing a targeting vector” renders the claim indefinite because it is unknown into what the targeting vector is introduced. Applicants have amended claim 20 to recite into what the targeting vector is introduced. Therefore this aspect of the rejection is no longer relevant.

With regard to claims 20 and 22, the Examiner asserted that the claims are indefinite in their recitation of the term “substantially” (homologous), which term is allegedly not explicitly defined and is inherently indefinite. Applicants disagree. However, the claims have been amended to no longer recite the term. Therefore, this aspect of the rejection is overcome.

Regarding claim 22, the Examiner has asserted that the claim is indefinite in that it recites the phrase “inserting a targeting vector” without specifying into what the targeting vector is introduced. The amendment to claim 22 overcomes this aspect of the rejection by reciting into what the targeting vector is introduced.

The Examiner has asserted that claim 24 is improperly dependent upon itself, which also affects claims 23 and 25, which are dependent upon claim 24. Applicants have overcome this rejection by the amending these claims to so that they depended from the method of claim 22.

### **Rejections under 35 U.S.C. § 102**

The Examiner has rejected claim 26 under 35 U.S.C. §102(b) as being anticipated by Capecchi *et al.* (AC; U.S. Patent No.: 5,627,059). Applicants respectfully traverse the rejection.

Claim 26 is drawn to an isolated host cell comprising a modification or disruption of a target gene, wherein the target gene is modified or disrupted by insertion of a targeting vector into the host cell.

According to the Examiner, Capecchi teaches the use of positive-negative targeting vectors that comprise targeting sequences flanking a positive selection marker and which further comprise a negative selection marker outside of the targeting cassette allowing for selection against random insertion events. Further, the Examiner asserts that Capecchi teaches examples where particular genes in a target cell have been inactivated by insertion of a targeting construct. Capecchi specifically relates to disruption of the *hox1.4* locus in mouse embryonic stem cells.

Applicants have amended claim 26, which now recites an isolated host cell comprising a modification or disruption of a target gene by insertion of the targeting vector of claim 1. As Capecchi has not taught or described the use of a targeting vector as recited in claim 1 to disrupt or modify a target gene in any cell, Capecchi fails to teach or suggest every claim limitation. Therefore, the rejection under 35 U.S.C. §102(b) has been overcome. Applicants respectfully request withdrawal of the rejection. Applicants submit that the cell as claimed in amended claim 26 is not anticipated by the teachings of Capecchi.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. RMES-02.

Respectfully submitted,

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Kelly L. Quast

Kelly L. Quast, Reg. No. 52,141  
DELTAGEN, INC.  
1031 Bing Street  
San Carlos, CA 94070  
(650) 569-5100